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**Bibliography**

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**DETAILED DESCRIPTION**

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[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the heterogeneity structure drug release device which emits a drug over a long period of time. Moreover, according to fluctuation of the symptom of the illness, this invention enabled it to control the blood drug concentration of a drug, i.e., it relates to the heterogeneity structure drug release device which answers fluctuation of the symptom of illnesses, such as inflammation, and emits a drug.

[0002]

[Description of the Prior Art] From the former, the polymeric materials of biodegradation nature are made into support (matrix), and the drug release device which made this distribute a drug is known. He makes hydrolysis decompose polymeric materials in the living body, and was trying to make a drug emit in the conventional drug release device. And since the polymeric materials needed to control the invasion rate of water when controlling a hydrolysis rate, all were hydrophobicity. Since there was a fault from which a deer is carried out, decomposition of these hydrophobic polymeric materials is the so-called bulk decomposition which advances by the whole polymeric materials, a crack and destruction occur in decomposition and coincidence, and surface area changes a lot, in the conventional drug release device, it was impossible to have made a drug emit based on the biodegradation of polymeric materials truly. Therefore, after carrying out the enthesi to in the living body, it was difficult to have controlled a drug again and to have made it emit to a long period of time based on the resolvability.

[0003] Moreover, according to fluctuation of the symptom of the illness, the drug delivery system which controls the drug concentration in blood is also known from the former. The matter which has the property which answers and carries out biodegradation to the signal which a living body emits as law based on a symptom on the other hand is used for support, and making a drug emit according to the decomposition is examined. Although various high polymers had been examined, by the matter which answers the temperature as a stimulus in the living body, hydrogen ion concentration (pH), etc., and controls drug release until now, each such drug release control was that to which it is going to change diffusion or the solubility of a drug by the high polymer. However, generally, since each of the decomposition devices depends these biodegradation nature high polymers on hydrolysis like \*\*\*\*, they are impossible for carrying out ON-OFF control of the resolvability in the living body. Furthermore, in such a biodegradation nature high polymer, since the hydrolysis rate was very slow compared with the invasion rate of the water to the inside of the high polymer ingredient, drug release was very difficult to be influenced also by change of the surface area by change (generation of a crack, destruction, etc.) of the configuration accompanying advance of disassembly of a high polymer ingredient, and to control the amount of drug release as a result. Therefore, control of the stimulus responsibility drug release by the biodegradable polymer matter was impossible as a matter of fact.

[0004]

[Problem(s) to be Solved by the Invention] This invention aims at offering the drug release device which has the function which answers a stimulus and can control emission of a drug further for the purpose of offering the drug release device which can control and emit a drug over a long period of time based on the resolvability of polymeric materials, after making polymeric materials into support and carrying out the enthesi to in the living body.

[0005]

[Means for Solving the Problem] Although all were hydrophobicity as mentioned above, the biodegradation nature high polymer used for the conventional drugs support this invention persons examine many things about use of the polymeric materials decomposed by devices other than the bulk decomposition in which these whole polymeric materials carry out hydrolysis advance uniformly. Use for support the hydrophilic polymer gel decomposed only from a front face, and things are thought of. By making it distribute, after making this hydrophilic polymer gel into support, making a drug contain in a microsphere and stabilizing, and nothing [ heterogeneity structure and nothing ], It had, the drug might be emitted over the long period of time, and this invention article which can moreover perform drug release rate-limiting with surface decomposition of polymeric materials was completed.

[0006] Furthermore, if the hydrophilic polymer gel decomposed by operation of the hydroxyl radical which is active oxygen generated transient only from a front face as a living body specific signal as hydrophilic polymer gel used for the above-mentioned support at the time of inflammation is used, this invention persons inflammation is answered, and decomposition of hydrophilic polymer gel can control emission of a drug by that of a line crack according to this decomposition, namely, emission of a drug can be controlled by the yield of a hydroxyl radical — thing knowledge was carried out and this invention was completed.

[0007] That is, this invention is a heterogeneity structure drug release device (claim 1) which makes support the hydrophilic macromolecule hydrogel decomposed from a front face, and is characterized by distributing a drug content microsphere in this support, and is a heterogeneity structure drug release device (claim 2) whose hydrophilic

macromolecule hydrogel decomposed from this front face is a hydrophilic macromolecule hydrogel decomposed from a front face according to an operation of a hydroxyl radical.

[0008] It explains in more detail about this invention. Generally the bulk decomposition system to which decomposition of the whole polymeric materials advances to homogeneity, the surface decomposition system in which decomposition advances only from the front face of polymeric materials, and these both mixed stock are known by the biodegradation of polymeric materials. The surface resolvability of an ingredient is indispensable to control the biodegradation nature of polymeric materials quantitatively and in time. Therefore, in the heterogeneity structure drug release device of this invention, the polymeric materials of the surface resolvability to which decomposition advances only from a front face are used. A deer is carried out, into the hydrophilic macromolecule hydrogel to which decomposition advances from this front face, a drug content microsphere is distributed and a drug can be emitted rate-limiting synchronizing with the so-called decomposition from the front face of the hydrophilic macromolecule hydrogel which is support when heterogeneity structuring is carried out. Therefore, emission of a drug is controllable by controlling surface decomposition of this hydrophilic macromolecule hydrogel.

[0009] A deer is carried out, and in the heterogeneity structure drug release device of this invention, if that to which the surface decomposition is performed over a long period of time as a hydrophilic macromolecule hydrogel is chosen or it controls to perform the surface decomposition over a long period of time, the drug release device which can perform emission of a drug over a long period of time will be obtained. Moreover, selection of that to which that surface decomposition answers a certain stimulus, and is performed as this hydrophilic macromolecule hydrogel obtains the drug release device which answers that stimulus and emits a drug. For example, the drug release device which will answer inflammation if the giant-molecule hydrogel in which an operation of active oxygen shows surface resolvability although active oxygen occurring transient from a leucocyte or a macrophage in inflammation, and having become the cause of the organization failure of versatility [ this ] is already known, namely, surface resolvability is specifically shown according to an operation of a hydroxyl radical is used for support, and emits a drug is obtained.

[0010] The hydrophilic giant-molecule hydrogels decomposed from the front face used by this invention are hydrophilic giant molecules, such as a polyethylene glycol and polyvinyl alcohol, at water-soluble polysaccharide, such as hyaluronic acid, a dextran, a carboxymethyl chitin, etc. over which the bridge was constructed, and a list. The cross linking agents used for bridge formation here are polyfunctional isocyanate, such as polyfunctional glycidyl ether, such as polyethylene glycol diglycidyl ether and polyglycerol polyglycidyl ether, and triisocyanate, etc. The surface decomposition is performed by the enzyme etc. over a long period of time, and each decomposes these hydrophilic macromolecule hydrogels for a short period of time specifically by the hydroxyl radical in the living body. Each gel water content of this hydrophilic macromolecule hydrogel is 50 - 99.8% desirably about 30 to 99.9%.

[0011] Moreover, in case a drug is made to emit by decomposition from the front face of a hydrophilic macromolecule hydrogel, in order to control this drug release quantitatively and in time, it is desirable to make the domain which was not made to carry out the homogeneity dissolution of the drug into gel, but contained the drug in high concentration form in consideration of the responsibility of drug release and prevention of the drug exsorption at the time of un-stimulating. As a drug content domain, after being emitted in the living body, what is absorbed or decomposed promptly is desirable. Then, it is made the gestalt of microsphere content of a drug and is made to distribute in a hydrophilic macromolecule hydrogel in this invention.

[0012] In this invention, although the drug content microsphere distributed in a hydrophilic macromolecule hydrogel is a particle which has required parent-hydrophobicity, stability, and biocompatibility when supporting a drug inside, for example, the macromolecule bead of absorptivity in the living body etc. can be considered, with a lipophilicity drug, the lipid microsphere of ribosome etc. is desirable in a water-soluble drug again. Moreover, although the magnitude (particle size) of the microsphere distributed in the hydrophilic macromolecule hydrogel changes with drug release patterns, particle size is usually 1.0 micrometers - about 100 micrometers desirably to 0.1 micrometers - about 10mm. Although microsphere concentration is based also on the particle size, it is about 5 - 10% desirably about 1 to 50%. And it is possible to change a drug release pattern with the magnitude of a microsphere.

[0013] In this invention, in order to make the macromolecule hydrogel decomposed from a front face distribute a drug content microsphere, various approaches are employable. It is desirable to adopt the approach of dissolving hydrophilic macromolecules, such as water-soluble polysaccharide, such as hyaluronic acid, a dextran, and a carboxymethyl chitin, or a polyethylene glycol, and polyvinyl alcohol, etc. in water, preparing a water solution, adding a drug content microsphere in this water solution, often being distributed, adding the \*\*\*\* cross linking agent subsequently described above, making carry out crosslinking reaction of the water soluble polymer, and making it hydrogel-ize.

[0014] Drawing 1 is a mimetic diagram for explaining an operation of the heterogeneity structure drug release device at the time of using the hydrophilic giant-molecule hydrogel which shows surface resolvability specifically by the hydroxyl radical as a hydrophilic giant-molecule hydrogel in the heterogeneity structure drug release device of this invention. 1 is the heterogeneity structure drug release device of this invention. The hydrophilic macromolecule hydrogel and 2' 2 indicates surface resolvability to be specifically by the hydroxyl radical are the decomposition product. 3 is a drug content microsphere. Now, if inflammation occurs in the living body, active oxygen will occur transient from a leucocyte or a macrophage. the whole surface 4 of the heterogeneity structure drug release device 1 with which this active oxygen was prescribed for the patient in the living body — contacting ( drawing 1 , a ) — the hydrophilic macromolecule hydrogel which constitutes the heterogeneity structure drug release device 1 decomposes from a front face according to an operation of this active oxygen. And a drug content microsphere is opened wide and emitted from a hydrophilic macromolecule hydrogel with this decomposition ( drawing 1 , b ).

[0015] Thus, in this invention, when a hydrophilic macromolecule hydrogel is decomposed from a front face, the drug content microsphere currently distributed is emitted rate-limiting synchronizing with decomposition. This is because dissolved a drug or did not only distribute it in the hydrophilic macromolecule hydrogel, and made the microsphere contain, and it was made to distribute in gel and was made the heterogeneity device gestalt, and the drug release nature

corresponding to the time of - un-decomposing of it becomes possible at the time of decomposition of a hydrophilic macromolecule hydrogel. Moreover, while eliminating the cell damage by the active oxygen generated by using the heterogeneity structure drug release device of this invention at the time of inflammation, it is expectable to demonstrate the pit inflammation operation by the steroid hormone emitted synchronizing with decomposition.

[0016] Moreover, by this invention, although drug release nature was greatly influenced by water solubility and the drug solubility called lipophilicity in the conventional biodegradation nature drug release system, since the hydrophilic macromolecule hydrogel of surface resolvability was distributed after making a microsphere contain a drug, a drug release rate can be specified, without being influenced by the drug properties of a drug, such as solubility. Furthermore, the decomposition device of a biolysis nature ingredient got down by hydrolysis, in the former, since the rate was slower than the permeation rate of the water to the inside of an ingredient, the drug activity fall before emission had become a problem, but drug activity can be held until it is emitted by distributing a biolysis nature ingredient, after making a microsphere contain a drug. Since the hydrophilic macromolecule hydrogel of surface resolvability was made to distribute it after this invention also made a microsphere contain a drug, drug activity can be held until it is emitted by hydrogel decomposition.

[0017]

[Example] Next, the example of reference and an example are shown and this invention is explained in more detail.

The example 1 (manufacture of a hydrophilic macromolecule hydrogel) of reference

1.0g (about 1 million presumed molecular weight) of hyaluronic acid was dissolved in 4.5ml of 1 convention sodium-hydroxide water solutions, and it fully deaerated with the aspirator. Ethylene-glycol-diglycidyl-ether 0.22g was dissolved in ethanol 0.5ml, it mixed with the hyaluronic acid solution quickly, and this was quickly poured in into the spacer with a thickness of 2mm. This was put for 15 minutes into the oven heated at 60 degrees C, and carried out crosslinking reaction. Bridge formation gel was immediately moved to the ethanol water solution 50% after that, trickled the hydrochloric acid and neutralized. A still newer ethanol water solution permuted gel 3 times. The obtained gel was transparent and colorless and the water content was 99.85% (HA1).

[0018] The example 2 (manufacture of a hydrophilic macromolecule hydrogel) of reference

1.0g (about 1 million presumed molecular weight) of hyaluronic acid was dissolved in 4.5ml of 1 convention sodium-hydroxide water solutions, and it fully deaerated with the aspirator. Ethylene-glycol-diglycidyl-ether 0.65g was dissolved in ethanol 0.5ml, it mixed with the hyaluronic acid solution quickly, and this was quickly poured in into the spacer with a thickness of 2mm. This was put for 15 minutes into the oven heated at 60 degrees C, and carried out crosslinking reaction. Bridge formation gel was immediately moved to the ethanol water solution 50% after that, trickled the hydrochloric acid and neutralized. A still newer ethanol water solution permuted gel 3 times. The obtained gel was transparent and colorless and the water content was 99.48% (HA3).

[0019] The example 3 (manufacture of a hydrophilic macromolecule hydrogel) of reference

1.0g (about 1 million presumed molecular weight) of HILARON acids was dissolved in 5.0ml of 1 convention sodium-hydroxide water solutions, and it fully deaerated with the aspirator. After mixing with the hyaluronic acid solution quickly and deaerating polyglycerol polyglycidyl ether, it poured in quickly into the spacer with a thickness of 2mm. This was put for 15 minutes into the oven heated at 60 degrees C, and carried out crosslinking reaction. Bridge formation gel was immediately moved to the ethanol water solution 50% after that, trickled the hydrochloric acid and neutralized. A still newer ethanol water solution permuted gel 3 times. The obtained gel was a frank color and the water content was 99.54% (HA9).

[0020] The example 4 (manufacture of a hydrophilic macromolecule hydrogel) of reference

Dextran (about 200,000 presumed molecular weight) 4.0g was dissolved in 18.0ml of 1 convention sodium-hydroxide water solutions, and it fully deaerated with the aspirator. Ethylene-glycol-diglycidyl-ether 1.92g was dissolved in ethanol 2.0ml, and this was poured in quickly [ it is quick and ] in mixing and a spacer with a thickness of 2mm with the dextran solution. This was put for 15 minutes into the oven heated at 60 degrees C, and carried out crosslinking reaction. Bridge formation gel was immediately moved to the ethanol water solution 50% after that, trickled the hydrochloric acid and neutralized. A still newer ethanol water solution permuted gel 3 times. A still newer ethanol water solution permuted the obtained gel 3 times. The obtained gel was colorless translucence and the water content was 85.40% (DEI).

[0021] 0.45g (about 1 million presumed molecular weight) of example hyaluronic acid was dissolved in 2.25ml of 0.5 convention sodium-hydroxide water solutions, and it fully deaerated with the aspirator. 400micro (Otsuka Pharmaceutical, trade name Intralipid, 20 % of the weight of concentration) of lipid pharmaceutical preparation I for intravenous injection was added as a lipid microsphere to this, and it mixed enough. Furthermore, polyglycerol-polyglycidyl-ether 0.61g was added, and after mixing quickly and deaerating, it poured in quickly into the spacer with a thickness of 2mm. This was put for 15 minutes into the oven heated at 60 degrees C, and carried out crosslinking reaction. Bridge formation gel was immediately moved to the ethanol water solution 50% after that, trickled the hydrochloric acid and neutralized. A still newer ethanol water solution permuted gel 3 times. The obtained gel was a frank color and the water content was 99.69% (HA10).

[0022] (Physical-properties trial of a hydrophilic macromolecule hydrogel and this invention product)

1. The hydrophilic macromolecule hydrogel (HA1, HA3) obtained in the above-mentioned examples 1 and 2 of reference was cut on the cube with a magnitude of 7x7x7mm, respectively, and the sample was created. It was immersed in FeSO4 water solution of 5mM(s) for two days, subsequently to the inside of 50microM and 100ml of M 500microH2O2 water solutions this each was put in, respectively, it agitated with the stirrer, and gel weight or the amount of gel decomposition in a solution was analyzed with time with a gravimetry and liquid chromatography. Dozens of hours decomposed the hydrophilic macromolecule hydrogel from several minutes, and each of the decomposition was in agreement with the rate equation when assuming surface decomposition so that drawing 2 and drawing 3 might show. Moreover, this catabolic rate was calculated with  $10^5 - 10^4$  cm/sec extent based on the rate equation (refer to Table 1). From not decomposing, in not pretreating these hydrophilic macromolecule hydrogels in FeSO4 water solution, this hydrophilic macromolecule

hydrogel is cut by having carried out surface decomposition by the hydroxyl radical.

[0023]

[Table 1]

コード	重量 (g)	H <sub>2</sub> O <sub>2</sub> 濃度 (μM)	Fe <sup>2+</sup> 濃度 (mM)	分解量 (%)	分解時間 (分)	分解速度 (cm/sec)
HA1	0.53	50	5.0	100	50	$1.4 \times 10^{-4}$
HA1	0.32	500	5.0	100	7	$8.1 \times 10^{-4}$
HA3	0.37	50	5.0	100	180	$3.3 \times 10^{-5}$
HA3	0.33	500	5.0	100	45	$1.3 \times 10^{-4}$

[0024] 2. The hydrophilic macromolecule hydrogel (HA3) obtained in the above-mentioned example 2 of reference was cut in magnitude of 20x20x6mm, and three samples were created. It was immersed in FeSO<sub>4</sub> water solution of 5mM(s) for two days, respectively. this — inside — one — a piece — a sample — first — purified water — 100 — ml — three — a minute — between — being immersed — subsequently — one — mM — H — two — O — two — a water solution — 100 — ml — three — a minute — between — being immersed — actuation — several times — repeating — weight change of gel in the meantime — having measured . About other two samples, replaced with 2OH<sub>2</sub> water solution of 1mM, and 100ml of 2OH<sub>2</sub> water solutions of 2mM(s) and 10mM(s) was used, respectively, and also it was operated similarly, and weight change of gel was measured, respectively. The result is shown in drawing 4 . Bridge formation gel shows a remarkable weight reduction only in H<sub>2</sub>O<sub>2</sub> water solution, and H<sub>2</sub>O<sub>2</sub> concentration effect of its weight reduction is carried out. It turns out that generating of a hydroxy radical was answered and ON-OFF of decomposition was controlled from not decomposing in not pretreating this bridge formation gel in FeSO<sub>4</sub> water solution.

[0025] 3. this invention article (HA10) which cut the hydrophilic macromolecule hydrogel (HA3) obtained in the above-mentioned example 2 of reference in magnitude of 7x7x7mm, and was obtained in the above-mentioned example was cut in magnitude of 20x10x1.8mm, and the sample was created. These samples were paid into the 0.14M phosphate buffer solution (pH7.4) of cow testis hyaluronidase — of predetermined concentration, respectively, and were agitated with the stirrer at 37 degrees C, and each gel weight change was analyzed with time. The result is shown in Table 2. It decomposed from several hours, having applied it for dozens of days, and could check that the decomposition was surface decomposition, and the catabolic rate was calculated with  $10^{-6}$  —  $10^{-8}$  cm/sec. Moreover, under the same conditions, disassembling hyaluronic acid non-constructed a bridge within several minutes was also checked, and it was shown that hyaluronic acid bridge formation gel (HA) has high resistance to hyaluronidase. Furthermore, when the hyaluronidase resolvability of HA3 and HA10 was compared, the catabolic rate of HA10 was small under the same conditions, and this showed that it was possible to raise hyaluronidase resistance in the living body with controlling the structure of cross linkage of gel by the chemical structure of a cross linking agent, even if it was the bridge formation gel of the same water content and the same amount of hyaluronic acid.

[0026]

[Table 2]

コード	形状	重量 (g)	ヒアルロニダーゼ濃度		分解量 (%)	分解時間 (時間)	分解速度 (cm/sec)
			unit/g	unit/ml			
HA3	立方体	0.064	$4.0 \times 10^4$	0.13	100	934	$5.98 \times 10^{-8}$
HA3	立方体	0.060	$8.0 \times 10^4$	0.25	100	432	$1.26 \times 10^{-7}$
HA3	立方体	0.023	$4.0 \times 10^5$	0.48	100	20	$1.97 \times 10^{-6}$
HA3	立方体	0.179	$1.6 \times 10^5$	1.5	100	25	$3.13 \times 10^{-6}$
HA3	立方体	0.180	$1.6 \times 10^6$	15	100	11	$7.13 \times 10^{-6}$
HA10	平板	0.687	$7.3 \times 10^4$	2.4	100	23	$3.14 \times 10^{-6}$
HA10	平板	0.661	$7.3 \times 10^5$	23	100	8.5	$8.50 \times 10^{-6}$
HA10	平板	0.616	$7.2 \times 10^6$	213	100	4.0	$9.03 \times 10^{-6}$
HA	-	0.005	$2.1 \times 10^4$	21	100	10-15分	-
HA	-	0.005	$4.1 \times 10^4$	41	100	2-3分	-
HA	-	0.010	$2.5 \times 10^5$	245	100	-2分	-

[0027] 4. The hydrophilic macromolecule hydrogel (DE1) obtained in the above-mentioned example 4 of reference was cut on the cube with a magnitude of 7x7x7mm, and it put in into the dextranase of predetermined concentration, and the 0.14M phosphate buffer solution (pH7.4), and agitated with the stirrer at 37 degrees C, and gel weight change was analyzed with time. Dextranase concentration decomposed from several, having bridge formation applied it for dozens of days. The result of this dextran bridge formation gel decomposition is shown in drawing 5 . This result was well in agreement with the theoretical formula when assuming that decomposition is surface resolvability, and the surface resolvability of dextran bridge formation gel was checked from this. Drawing 6 shows this. As for catabolic rate here, dextranase concentration was calculated in 1.5 and 15 unit(s)/ml with  $2.6 \times 10^{-8}$  and  $8.8 \times 10^{-8}$  cm/sec, respectively. Moreover, under the same conditions, decomposing the dextran non-constructed a bridge in a short time was also checked, and it was shown that dextran bridge formation gel has high resistance to a dextranase. Dextran bridge formation gel is a giant-molecule hydrogel decomposed from a front face over a long period of time in the living body, and this shows that it is useful as a microsphere content heterogeneity device.

[0028] 5. this invention product (HA10) obtained in the above-mentioned example was cut to plate-like [ with a magnitude of 20x10x1.8mm ], and it put in into the 0.14M phosphate buffer solution (pH7.4) of cow testis hyaluronidase - of predetermined concentration (2.4u/ml, 23u/ml), and agitated with the stirrer at 37 degrees C, and gel resolvability and the microsphere emission nature at that time were analyzed with time by weight change and the solution turbidmetry of gel, respectively. As were shown in drawing 7 , and HIARONIDA-ZE concentration decomposed gel with constant speed over dozens of hours from several hours and it was shown in drawing 8 , microsphere emission at that time was also performed with constant speed synchronizing with decomposition. this — the microsphere in this invention article — surface decomposition of gel — it having been rate-limiting and having been emitted is shown.

[0029] 6. The hydrophilic macromolecule hydrogel (HA3) obtained in the above-mentioned example 2 of reference was cut on the cube with a magnitude of 7x7x7mm, and \*\*\*\*\* was put in into rabbit ischemia scutellum plasma, it agitated with the stirrer at 37 degrees C, and gel weight change was analyzed with time. although gel showed about 10% of weight reduction until after 1 hour at the latest — immediately after immersion, weight did not change until after 160 hours after it. Although it contracts with ionic strength since hyaluronic acid bridge formation gel is electrolyte gel, for that reason, the weight reduction in this case is also considered. Therefore, it turns out that this hyaluronic acid bridge formation gel has high resistance to a plasma component.

[0030] 7. The hydrophilic macromolecule hydrogel (HA3, HA9) obtained in the above-mentioned examples 2 and 3 of reference was cut in magnitude of 20x10x2mm, wet sterilization was carried out for 60 minutes, and 120 degrees C of hyaluronic acid quanta by the gel gravimetry and the carbazole method were performed about each. At HA3, reduction of the increment in weight and the amount of hyaluronic acid was accepted by the above-mentioned sterilization, and the difference with as significant weight and amount of hyaluronic acid as sterilization before was not accepted by HA10 to disassembly of the hyaluronic acid which is about 20% having been shown. This shows that the behavior at the time of sterilization changes with classes of cross linking agent used for bridge formation, even if water content and the amount of hyaluronic acid are the same bridge formation gels.

[0031] 8. The hydrophilic macromolecule hydrogel (HA9) obtained in the above-mentioned example 3 of reference was \*\*\*\*\*(ed) to hypodermically [ healthy rat regions-of-back ], and stability in the living body was examined. Immediately after cutting open the Wister system male rat (five weeks old) regions of back under anesthesia by pentobarbital intraperitoneal injection and inserting 20x10x1.8mm bridge formation gel (HA10) here, the incision part was sutured with No. 3 silk thread. Although especially insertion gel was not fixed, the incision part was sutured, after suturing two connective tissue between an incision part and gel with No. 5 nylon yarn so that gel may not move to an incision suture part. After a \*\*\*\* fixed period, the back \*\*\*\* gel which euthanized the rat by a lot of pentobarbital intraperitoneal injection was extracted from hypodermically, and the quantum of the amount of residual gels was immediately carried out by the carbazole method. Moreover, after a fixed period, the skin which adjoined the \*\*\*\* part was surgically cut open, the load of the wound by operative stress was carried out, inflammation was made to cause, it extracted from hypodermically after one week, and the quantum of the amount of residual gels was carried out similarly.

[0032] Although the about 20% of hyaluronic acid bridge formation gel was decomposed about one week after the operation, it is comparatively stable over a long period of time after that, and, in all, the about 70% remained. The effect of the connective tissue on a gel \*\*\*\* perimeter was accepted in neither of the cases at all with the macro-scopic view. Moreover, by carrying out the load of the wound to a rat, about 20% of \*\*\*\* gel was decomposed further ( drawing 9 ). It was checked that bridge formation hyaluronic acid gel answered the wound healing of a back cut part just behind \*\*\*\*, decomposed it, and about 20% had decomposed further by inflammation inducement from the outside from this. [ about 20% of ] As mentioned above, this hyaluronic acid bridge formation gel is considered to answer the hydroxyl radical to generate immediately and to be decomposed into it at the time of inflammation, although it is very stable at the time of healthy and decomposes into it over a long period of time.

[0033]

[Effect of the Invention] Since the heterogeneity structure drug release device of this invention made support the hydrophilic macromolecule hydrogel decomposed from a front face, distributed the drug content microsphere and was made into heterogeneity structure into this support, it can emit a drug rate-limiting synchronizing with the decomposition from the front face of this hydrophilic macromolecule hydrogel. Therefore, emission of a drug is controllable by controlling surface decomposition of this hydrophilic macromolecule hydrogel. That is, if that to which the surface decomposition is performed over a long period of time as a hydrophilic macromolecule hydrogel is chosen or it controls to perform the surface decomposition over a long period of time, the drug release device which can perform emission of a drug over a long period of time will be obtained. Moreover, if the surface decomposition uses for support the giant-molecule hydrogel which shows surface resolvability specifically according to an operation of the hydroxyl radical generated transient in a certain stimulus, for example, inflammation, the drug release device which answers inflammation and emits a drug will be obtained.

[0034] Therefore, the heterogeneity structure drug release device of this invention can perform emission of a drug over a long period of time, and answers extent of symptoms, such as inflammation, and can control the burst size of a drug. Furthermore, it has high resistance to a plasma component, and while stability in the living body is good, and \*\*\*\* is possible for it over a long period of time and it can maintain the activity of a bioactive drug highly till emission, corresponding to restrictive surface decomposition of gel, ON-OFF control of the drug release nature at the time of - un-generating can be carried out at the time of living body signal generating. Furthermore, since the amount of drug release by decomposition of a macromolecule hydrogel is controllable with the surface area of gel, the amount of drug release can be predicted from the early stages of decomposition to the last stage as a function of surface area. Thus, the heterogeneity structure drug release device of this invention is very useful.

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**DESCRIPTION OF DRAWINGS**

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**[Brief Description of the Drawings]**

- [Drawing 1] The model Fig. showing an operation of the heterogeneity structure drug release device of this invention
- [Drawing 2] The graph which shows the resolvability of the hyaluronic acid bridge formation gel by the hydroxyl radical
- [Drawing 3] The graph which shows the catabolic rate of the hyaluronic acid bridge formation gel by the hydroxyl radical
- [Drawing 4] The graph which shows the hydroxyl radical responsibility surface resolvability of hyaluronic acid bridge formation gel
- [Drawing 5] The graph which shows the resolvability of the dextran bridge formation gel by the dextranase
- [Drawing 6] The graph which shows the catabolic rate of the dextran bridge formation gel by the dextranase
- [Drawing 7] The graph which shows the surface resolvability of the hyaluronic acid bridge formation gel by hyaluronidase
- [Drawing 8] surface decomposition of hyaluronic acid bridge formation gel — the graph which shows rate-limiting microsphere emission behavior
- [Drawing 9] The graph which shows the biodegradation nature and its inflammation responsibility of rat entheses hyaluronic acid bridge formation gel

**[Description of Notations]**

- 1 Heterogeneity Structure Drug Release Device
- 2 Hydrophilic Macromolecule Hydrogel
- 3 Drug Content Microsphere

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[Translation done.]

**\* NOTICES \***

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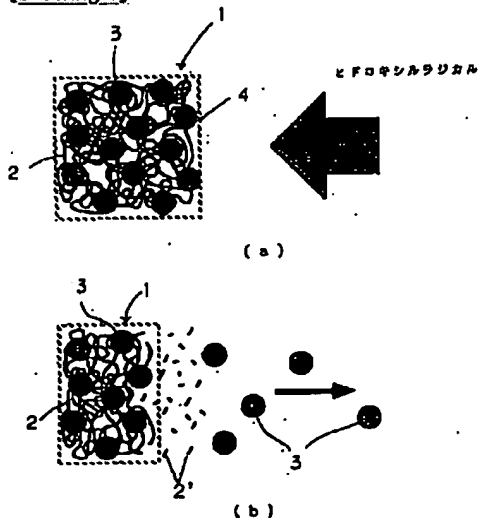
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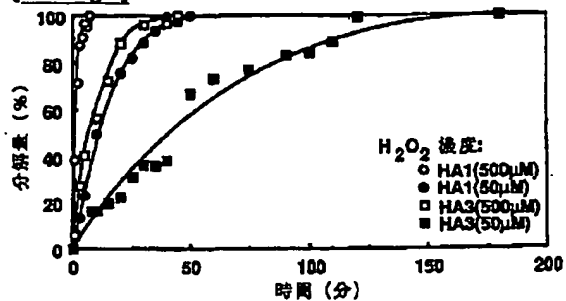
**DRAWINGS**

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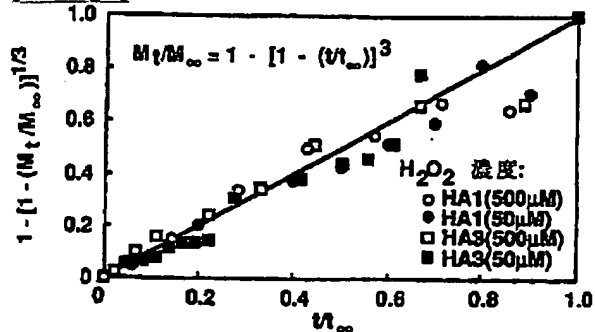
**[Drawing 1]**



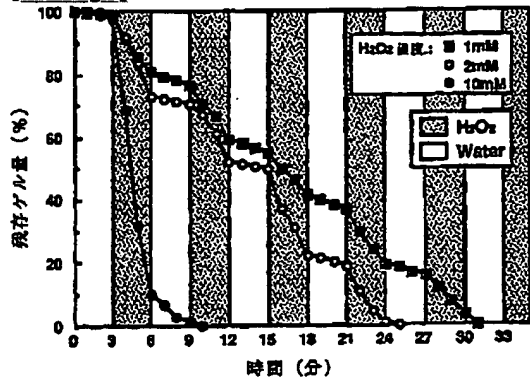
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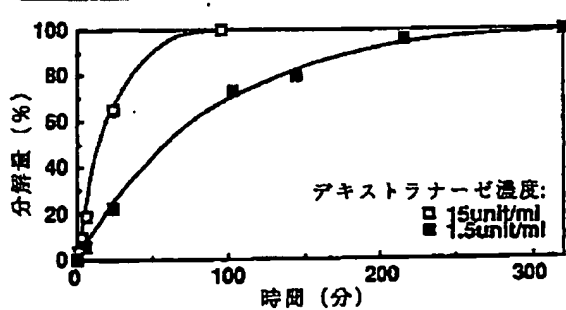
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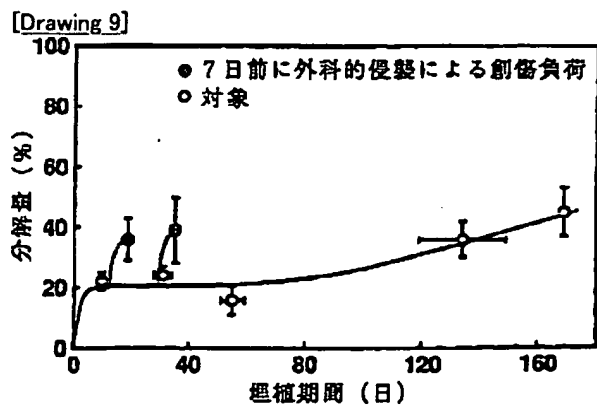
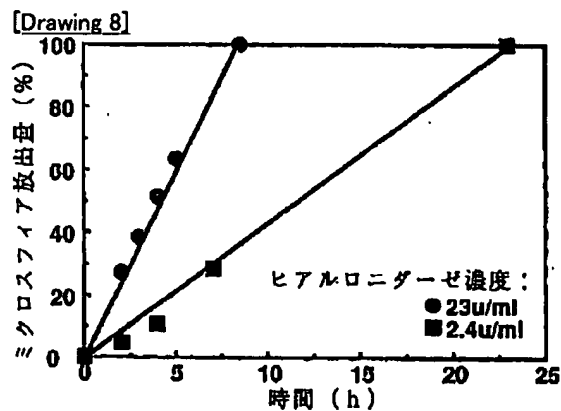
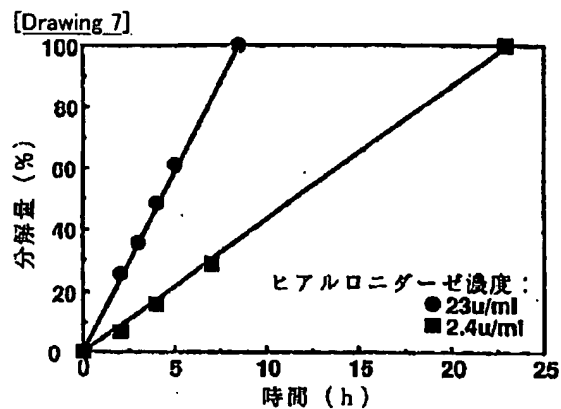
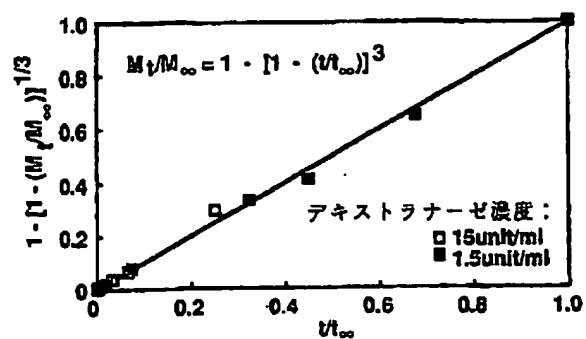
[Drawing 4]



[Drawing 5]



[Drawing 6]



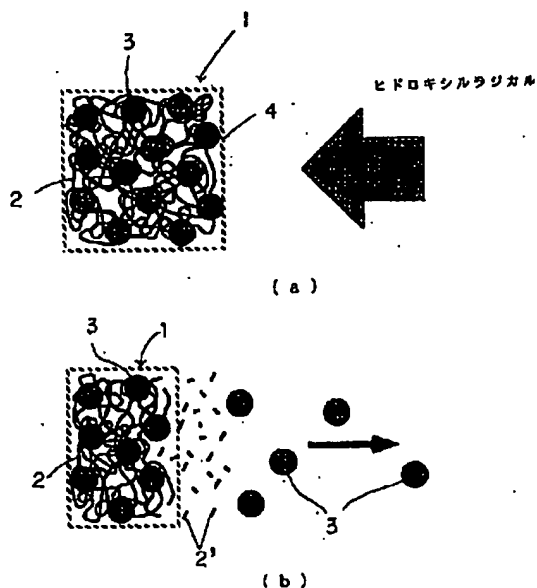
[Translation done.]

## Epitome

### (57) [Abstract]

[Objects of the Invention] The heterogeneity drug release device which has the function which emits a drug over a long period of time, and answers a stimulus of inflammation etc., and controls emission of a drug is offered. [Elements of the Invention] It is the heterogeneity drug release device which the hydrophilic macromolecule hydrogel which a front face decomposes is made [ device ] into support, and makes it come to distribute a drug content microsphere in this support. If the hydrophilic giant-molecule hydrogel 2 which a front face decomposes by the hydroxyl radical is used as a hydrophilic giant-molecule hydrogel, the hydrophilic giant-molecule hydrogel 2 will decompose from a front face, and the drug content microsphere 3 will be emitted from the heterogeneity drug release device 1 with this decomposition by the hydroxyl radical 4 produced at the time of a living body's inflammation.

[Translation done.]



[Translation done.]

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## CLAIMS

### [Claim(s)]

[Claim 1] The heterogeneity structure drug release device which makes support the hydrophilic macromolecule hydrogel decomposed from a front face, and is characterized by distributing a drug content microsphere in this support.

[Claim 2] The heterogeneity structure drug release device according to claim 1 whose hydrophilic giant-molecule hydrogel decomposed from a front face is a hydrophilic giant-molecule hydrogel decomposed from a front face according to an operation of a hydroxyl radical.

[Translation done.]